

REMARKS

Formal Matters

Applicants amended claims 1 and 4-9. No new matter has been introduced by way of these amendments. Applicants also canceled claims 2 and 3. New claims 23-25 were added by the Applicants. Support for new claims 23-25 may be found in the specification, for example, at page 12, line 19 to page 14, line 4 or at original claim 4.

Claims 1, 4-11, and 23-25 are now pending in this application.

Enablement Rejections

Claims 1-11 were rejected by the Examiner because the specification allegedly does not reasonably provide enablement to make or use the present invention. Office Action at pages 3-5. Specifically, claim 6 was rejected by the Examiner under 35 U.S.C. § 112 because it is allegedly not clear from the disclosure that the deposit of the hybridoma clone which produces the #23-57-137-1 antibody meets all the criteria set forth in 37 C.F.R. § 1.801-1.809. Office Action at pages 3-4. In response, Applicants file the attached Microorganism Deposit Declaration under 37 C.F.R. § 1.808(a). Thus, Applicants submit that the rejection of claim 6 has been obviated and request that the rejection be withdrawn.

The Examiner also rejected the claims because allegedly "given the indefinite number of undisclosed 'substance', 'antagonist', it is unpredictable which undisclosed substance or antagonist would bind to PTHrP." Office Action at page 5. Further, the Examiner stated that because "the binding specificity of the antibody in the claimed methods is not enabled, it follows that any monoclonal antibody, any antibody fragment

instead of the binding fragment, chimeric antibody, and humanized antibody for the claimed methods are not enabled.” *Id.* Applicants respectfully traverse. Although Applicants believe that these concepts are supported by the specification, Applicants have replaced the word “substance” in independent claims 1 and 9 with “anti-PTHrP antibody.” Further, Applicants have canceled claims 2 and 3, which do not further limit the claims as amended. Applicants reserve the right to pursue the canceled subject matter in a separate application.

One of skill in the art would be able to make and use the claimed invention, as amended, using the following teachings in the application as a guide:

- A description of antibodies and methods of making them is provided on pages 4-5 of the specification. A specific example of an antibody, #23-57-137-1, is also provided along with information regarding its deposit under Accession No. FERM BP-5631.
- The specification at pages 5-8 teaches how a monoclonal antibody-producing hybridoma can be prepared.
- The production of recombinant antibodies is taught at pages 8-10.
- The preparation of modified antibodies and fragments of antibodies is discussed at pages 12-14.
- Expression, production, isolation, and purification of recombinant or modified antibodies are detailed at pages 14-16.
- Determination of the binding activity and neutralizing activity of an antibody is taught at page 16.

- Pages 16-18 describe routes of administration, dosage, and pharmaceutical preparations, including pharmaceutical carriers and additives.
- Examples 1-2 (specification at pages 19-23) teach administration of a humanized anti-PTHrP antibody to human tumor-transplanted rats. Examples 1-2 teach that administration of the antibody ameliorated decreased blood vasopressin levels, polyuria, and increased blood osmotic pressures. See Figures 1-4.

One of ordinary skill in the art based on these teachings would be able to both make and use the antibodies of the invention. In light of the amendment to claims 1 and 9, and these arguments, Applicants request that the Examiner withdraw this rejection.

Written Description Rejection

Claims 1-5 and 7-11 have been rejected by the Examiner under 35 U.S.C. § 112 as allegedly “containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.” Office Action at page 6. Applicants respectfully traverse this rejection. Applicants note, as discussed above, that claims 2 and 3 have been canceled without prejudice or disclaimer. Further, claims 1 and 9 have been amended by replacing the word “substance” with the phrase “anti-PTHrP antibody,” which was previously recited in claim 3.

The Examiner’s position is inconsistent with the Office’s Synopsis of Application of Written Description Guidelines, which indicates that written description can be met by

Show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Guidelines, 66 Fed. Reg. at 1106 (emphasis added). Section 2163 of the M.P.E.P., which discusses these guidelines, states that “disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen.” (citing *Noelle v. Lederman*, 355 F.3d 1343, 1349 (Fed. Cir. 2004) (“[A]s long as an applicant has disclosed a ‘fully characterized antigen,’ either by its structure, formula, chemical name, or physical properties . . . the applicant can then claim an antibody by its binding affinity to that described antigen”)). Applicants respectfully submit that the structure of full-length PTHrP was known in the art at the time the application was filed. Further, the specification contains an actual reduction to practice of the claimed invention, which demonstrates that an anti-PTHrP antibody maintains or increases vasopressin level in an animal model of hypercalcemia. See specification at pages 19-24.

Moreover, the Office has not met its burden with respect to this rejection.

M.P.E.P. § 2163.04 states:

A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a

preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97.

The Examiner has not provided a reasonable basis to challenge the adequacy of Applicants' written description. The Examiner's isolated reasoning that the specification lacks written description because of "the lack of any additional parathyroid hormone related peptide (PTHrP) to which the antibody binds in the claimed method" is insufficient. Office Action at page 6. It is not necessary to show that the antibody binds to any other PTHrP antigens. The law allows applicants to claim antibodies to a fully characterized antigen. There is no evidence of record that a person skilled in the art would not recognize in Applicants disclosure a description of the invention defined by the claims. Applicants therefore assert that the claims, as amended, fulfill the written description requirement and request that the Examiner withdraw this rejection.

Indefiniteness Rejections

Claims 1-11 have been rejected by the Examiner under 35 C.F.R. § 112, second paragraph as being indefinite because they fail to point out and distinctly claim the subject matter defined as the invention. Specifically, the Examiner alleges that "[t]he recitation of 'a receptor thereof' in claims 1 and 9 is indefinite and ambiguous . . . since there is more than one receptors to which the PTHrP binds." Office Action at page 7. Applicants respectfully traverse. At page 3, lines 16-19 of the specification the term "PTHrP receptor" is defined as "any receptor that can bind to PTHrP (such as those described in Japanese National Phase Laid-open Publication No. 6-506598)." In addition to interpreting the claim in light of the specification, claim language must also

be analyzed by the teachings of the prior art and as one of ordinary skill in the art would understand the claim. The term "PTHrP receptor" is understood with a reasonable degree of clarity by one of ordinary skill in the art to mean a structure on the surface of a cell (or inside a cell) that selectively receives and binds a specific substance. Further, specific receptors for PTHrP have been identified in the literature, for instance in Japanese National Phase Laid-open Publication No. 6-506598. Applicants therefore respectfully request that the rejection be withdrawn.

The Examiner also rejected claim 4 because allegedly the "antibody has the binding fragment and the Fc fragment and it is not clear which fragment of the antibody applicant intends to claim." Office action at page 7. Further, the Examiner states "it is not clear which 'modified form of the fragment' that is part of the claimed invention." *Id.* Applicants respectfully traverse. At page 12, lines 21-23 of the specification a fragment is defined as "Fab, F(ab')₂, Fv, or a single chain Fv (scFv) composed of a H-chain Fv fragment and a L-chain Fv fragment linked together through a suitable linker." The modified form of such a fragment is also defined in the specification. For example, at the paragraph spanning page 13-14 the specification reads: "As a modified form of the above-mentioned antibodies, for example, an anti-PTHrP antibody conjugated to any molecule (e.g., polyethylene glycol) may also be used."

In addition to interpreting the claim in light of the specification, claim language must also be analyzed by the teachings of the prior art and as one of ordinary skill in the art would understand the claim. The term "antibody fragment" is understood with a reasonable degree of clarity by one of ordinary skill in the art to mean a portion of an

antibody that retains binding specificity for a particular antigen. The Harlow *et al.* reference (in *Antibodies a Laboratory Manual*, 1988, Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, pages 626-629) provided by the Examiner, for instance, discloses Fab, Fc and F(ab)₂ fragments and a method of isolating Fab fragments. In addition, teachings of the prior art define different parts of an antibody, such as Fab and scFv that conform to this definition. Indeed, the specification recites at page 12, lines 19-21 that an antibody within the scope of the invention encompasses any fragment or modified product of a fragment that can “bind to PTHrP and inhibit the activity of the PTHrP.” Finally, Applicants add dependent claim 25 to more clearly describe these particular fragments and dependent claims 23 and 24 to more particularly describe the modified fragments. Applicants therefore respectfully request that the rejection be withdrawn.

The Examiner rejected claim 6 as being indefinite, because the #23-57-137-1 antibody is “merely a laboratory designation that does not clearly define the product in the claimed method.” Office Action at page 7. Applicants respectfully traverse. The hybridoma clone #23-57-137-1 is clearly described in the specification along with deposit information under the terms of the Budapest Treaty. See, *e.g.*, specification at page 5, lines 7-11; page 24, lines 21-25; page 29, lines 1-7; page 30, Table 1. However, merely to expedite prosecution, Applicants have amended claim 6 to recite the Deposit Accession Number. Applicants respectfully request that the rejection be withdrawn.

Anticipation Rejection

The Examiner rejected claims 1-2 as being anticipated under 35 U.S.C. § 102(b) by Yamamoto *et al.* (Endocrinology 138(1):383-388). The Examiner further asserts that “Yamamoto *et al.* teach a method of increasing low vasopressin level in a patient such as rat by administering to said patient at least one substance such as PTHrP(1-34) fragment.” Office Action at page 8. As described above, Applicants have canceled claim 2 without prejudice. Claim 1 has been amended to recite that the substance capable of inhibiting binding is an anti-PTHrP antibody, further defining the scope of the claim. Yamamoto *et al.* do not disclose the administration of a PTHrP antibody to maintain or increase vasopressin level, but only teach the use of a PTHrP(1-34) fragment. Therefore, Applicants request that the Examiner withdraw this rejection.

Obviousness Rejections

The Examiner rejected claims 1, 3-4, and 7-11 under 35 C.F.R. § 103(a) as being unpatentable over Yamamoto *et al.*, in view of Sato *et al.*, Harlow *et al.* and Hotta *et al.* Office Action at page 9. The Examiner also rejected claim 5 under C.F.R. § 103(a) as being unpatentable over Yamamoto *et al.*, in view of Sato *et al.*, Harlow *et al.* and Hotta *et al.* as applied to claims 1, 3-4, and 7-11 and further in view of U.S. Patent No. 6,180,370B. Office Action at page 11. Specifically, the Examiner states that “it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the substance that inhibits the binding between PTHrP and a receptor as taught by Yamamoto *et al.* for the substance such as the monoclonal antibody that binds

to PTHrP (1-34) as taught by Sato et al.” Office Action at page 10. Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) all claim limitations must be taught or suggested, (2) there must be some suggestion or motivation to modify the references or combine reference teachings, and (3) there must be a reasonable expectation of success. M.P.E.P. § 2143.03.

Applicants respectfully submit that the cited references do not teach or suggest all claim limitations. Yamamoto *et al.* teaches that a fragment of PTHrP, PTHrP(1-34), functions in the brain through a novel receptor distinct from the PTH/PTHrP receptors described previously. See Yamamoto *et al.*, abstract. In this distinct functionality of the PTHrP(1-34) fragment, the N-terminus of the fragment has been demonstrated to contain the bioactive region. Yamamoto *et al.* compares the PTHrP(1-34) fragment to another fragment missing the N-terminal region, PTHrP(7-34), finding that only PTHrP(1-34) stimulates AVP release in the brain. (See Yamamoto *et al.*, paragraph spanning pages 387-388 (stating “the bioactivity of PTHrP (1-34) on AVP secretion from the rat SON is located in the N-terminus and it binds to the receptors at the C-terminus”)).

In fact, PTHrP(7-34) binds to the same novel receptor as PTHrP(1-34), but does not contain the active site, and thus is a competitive inhibitor of PTHrP(1-34). See *also Id.*, page 385, right column, “Effect of PTHrP(7-34) on PTHrP(1-34)-induced AVP secretion.” Yamamoto *et al.* states that the binding site for the novel receptor is located at the C-terminus, or shared portion of these two sequences. As PTHrP(7-34) inhibits

the effect of PTHrP(1-34), this demonstrates that PTHrP(1-34) is having an independent biological effect on a novel receptor and is not merely a competitive inhibitor of the binding of full length PTHrP to the previously known type I and type II receptors.

Yamamoto *et al.* does not teach or suggest the use of a PTHrP fragment as a competitive inhibitor of binding of the full length PTHrP protein to the previously described type I or type II receptors. The Yamamoto *et al.* reference refers to a distinct effect of the PTHrP(1-34) fragment, which is unrelated to the binding of full length PTHrP to the type I and type II receptors. Given the fact that Yamamoto *et al.* fully describes the mechanism of action of the PTHrP(1-34) fragment, even if the novel receptor is not fully characterized, Applicants assert that the Office's statement that the PTHrP(1-34) fragment is a competitive inhibitor of the binding of the full length PTHrP protein to a type I or type II receptor is not supported by the record.

Furthermore, Sato *et al.* does not teach or suggest maintaining or increasing vasopressin levels using an anti-PTHrP antibody. As the Examiner states, Sato *et al.* teach that a "monoclonal antibody to PTHrP (1-34) inhibits the binding between PTHrP and its receptor [and] led to a decrease in serum calcium, increase in body weight and survival of nude mice bearing PTHrP producing tumors." Office Action at page 10. The reference does not discuss vasopressin levels, nor the effect of PTHrP/PTHrP receptor binding on such levels. Thus, Yamamoto *et al.* and Sato *et al.*, taken together, do not teach or suggest increasing or maintaining vasopressin level by administering an antibody that inhibits the binding between PTHrP and a receptor thereof.

The Examiner states that Harlow *et al.* teach that “problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies.” *Id.* Further, Hotta *et al.* teach “symptoms associated with increased hypercalcemia and decrease in vasopressin level.” *Id.* Finally, the ‘370 patent allegedly “teaches a method of producing chimeric antibodies and humanized antibodies.” Office Action at page 11 (citations omitted). These references do not cure the defects described above. Applicants therefore respectfully request that the Examiner withdraw these obviousness rejections.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

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By: Amy E. Purcell
Amy E. Purcell
Reg. No. 53,492